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Canadian Adverse Reaction Newsletter

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Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge
Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Transdermal fentanyl (Duragesic) : abuse in adolescents

Duragesic (fentanyl transdermal system) has been marketed in Canada since 1992 and is indicated for the management of chronic pain in patients requiring continuous opioid analgesia for pain that is not optimally managed with weak or short-acting opioids.[1] Opioid-naive patients may be at risk of overdose with the use of opioid drugs, including fentanyl.

From Jan. 1, 1998, to Jan. 31, 2005, Health Canada received 4 reports of abuse of Duragesic patches by adolescent boys aged 14–17 years. Three of the boys died, and 1 had not recovered at the time of reporting. The patches were found either in home medicine cabinets or were prescribed to a parent. In 3 cases the use of marihuana was reported.

From 28% to 84% of the active ingredient may be recovered from a fentanyl transdermal system even after 3 days of therapeutic use, which is more than sufficient drug for potential abuse.[2] The fentanyl from the patch can be abused by ingestion, intravenous injection, volatilization and inhalation, or application of multiple patches, and such abuse may result in death.[3-5] Potential for overdose also exists when heating pads are applied to the skin to raise skin temperature and increase the rate of fentanyl absorption from the patch.[6,7] In addition, low concentrations of fentanyl are sufficient to induce respiratory depression.[8]

Abuse of fentanyl patches depends on access to improperly discarded or secured patches. The Canadian product monograph provides recommendations for the safe disposal of Duragesic patches. Specific information for the patient details the risks of Duragesic and how to apply, remove and dispose of the transdermal patches.[1] Safe and secure dispensing, storage and disposal measures must be reinforced for patients, pharmacists and physicians.

Barbara Raymond, BSc, MD, Health Canada

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Black cohosh: international reports of liver toxicity

Black cohosh (*Cimicifuga racemosa*) is an herbal medicine used mainly to alleviate menopausal symptoms. Adverse reactions (ARs) to black cohosh include gastrointestinal irritation, headache, dizziness and vomiting.[1] Recently, there have been international case reports of liver dysfunction suspected to be associated with its use.

As of March 31, 2005, the United Kingdom's Medicines and Healthcare products Regulatory Agency received 20 reports of liver reactions suspected of being associated with the use of black cohosh.[1,2] The cases ranged in severity from abnormal liver function test results to various forms of hepatitis. At the time of reporting, most of the patients had recovered or were recovering. In addition, a case of hepatic failure associated with the use of black cohosh was recently published.[3]

From Jan. 1, 1998, to Feb. 28, 2005, Health Canada received 7 reports of ARs suspected of being associated with ingestion of black cohosh. There were no reports of liver dysfunction. All of the cases involved women, aged 33 to 55 years. Some of the ARs reported included dizziness, rash, pruritus, edema, increased pulse rate, bradycardia, atrial fibrillation, changes in serum thyroid levels, vaginal bleeding and convulsions. Causality could not be assigned specifically to black cohosh because most of the reports contained insufficient clinical information and lacked details on the use of concomitant medications.

Since January 2004, all natural health products, including those containing black cohosh, are covered under the new Natural Health Products Regulations. Health Canada encourages health care providers and the public to report any suspected ARs related to natural health products to Health Canada.

Chad Sheehy BSc, ND; Mano Murty MD, CCFP, FCFP; Karen Pilon, RN, Health Canada

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3. Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. *Dig Dis Sci* 2005;50(3):538-9.

Rosiglitazone (Avandia): decreased high-density lipoprotein cholesterol levels

Rosiglitazone (Avandia) is a member of the thiazolidinedione family of oral hypoglycemic agents used to improve glycemic control by increasing insulin sensitivity in muscle and adipose tissue and inhibiting hepatic gluconeogenesis.[1] It has been marketed in Canada since March 2000.

Clinical trials using rosiglitazone as monotherapy detected increases in levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and decreases in levels of free fatty acids.[1] Decreased HDL-C levels were not seen in over 1400 patients treated with rosiglitazone in clinical trials.[2] It is noteworthy that fibrates generally have a beneficial effect on HDL-C and triglyceride levels but occasionally have been associated with decreases in HDL-C and apolipoprotein A-I concentrations.[2]

From Jan. 1, 2000, to Dec. 31, 2004, Health Canada received 1 report of a decreased HDL-C level suspected of being associated with rosiglitazone. A 61-year-old woman with type 2 diabetes, hyperlipidemia, diabetic retinopathy and nephropathy had been taking fenofibrate, metformin and glyburide for more than 1 year, and perindopril for 9 months, before starting rosiglitazone therapy, 8 mg daily. The serum HDL-C level at this time was 1.06 mmol/L. Approximately 3 months later the HDL-C level had decreased to 0.27 mmol/L, the triglyceride level had increased from 1.4 to 3.4 (target level in high-risk patients < 1.5) mmol/L, and the total cholesterol:HDL-C ratio increased from 4 to 15.4 (target level in high-risk patients < 4). Following discontinuation of the rosiglitazone therapy after 7 months of use, there was an increase in the HDL-C level to 0.8 mmol/L and a reduction in the total cholesterol: HDL-C ratio to 5.3. The abnormal lipid values resolved 2 months after stopping the rosiglitazone therapy. The reporter did not state whether treatment with fenofibrate was continued. Subsequently, the patient developed symptoms of angina and underwent angioplasty.

The medical literature describes 3 cases of profound decreases in HDL-C and apolipoprotein A-I concentrations during treatment with rosiglitazone.[2] Triglyceride levels also increased during treatment. In all 3 cases, the HDL-C level increased after withdrawal of the rosiglitazone. Two patients were taking a fibrate but did not have a decreased HDL-C level until rosiglitazone was introduced.

Given the findings of the 3 cases from the medical literature and the Canadian case, in patients prescribed rosiglitazone, it would be advisable to measure baseline HDL-C and triglyceride levels and check them again shortly after the start of therapy.

Debra Willcox BSP, Health Canada

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1. *Avandia (rosiglitazone)* [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2004.
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Ibuprofen: Stevens–Johnson syndrome

Stevens–Johnson syndrome (SJS) is a severe blistering rash affecting both skin and mucous membranes. The majority of cases have been attributed to drug exposures.[1,2] The reaction begins with burning and painful lesions on the face and upper torso and extends to the rest of the body. Blistering and epidermal detachment may occur.[1–3] Patients may present with fever, malaise, myalgia and ocular manifestations. Mortality has been estimated at 5% of cases.[3,4]

From Jan. 1, 1973, to Feb. 21, 2005, Health Canada received 4 reports of SJS suspected of being associated with ibuprofen. At the time of reporting, 3 patients had not recovered, and the outcome was unknown for 1 patient. The reports involved patients aged 13 to 34 years and were all received after April 2001. The dosages ranged from 200 mg to 1200 mg daily. The onset of reactions varied from the day of administration to approximately 15 days after starting ibuprofen. In one report, carbamazepine was indicated as a suspect drug along with ibuprofen.

Ibuprofen has been available over the counter since August 1989. SJS is listed in the product monographs for ibuprofen products.[5,6] Although cases of SJS remain rare, patients taking ibuprofen should be warned to discontinue use and seek medical attention should any rash, fever without an alternative explanation or mucosal symptoms develop.[2]

Sally Pepper, BScPhm, Heather Morrison, BSc (Biology), MLIS, Health Canada

References

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New Regional Adverse Reaction Centres

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP), a program of Health Canada's Marketed Health Products Directorate, is pleased to announce the establishment of two new Regional Adverse Reaction (AR) Centres, one in Alberta and one in Manitoba. They have joined the existing Regional AR Centres — currently located in British Columbia, Saskatchewan, Ontario, Quebec and Atlantic Canada — as the regional points-of-contact for the CADRMP. As of April 2005, health care professionals and consumers in Alberta and Manitoba can report ARs to these new centres using the program's toll free numbers:

Tel: 866 234-2345
Fax: 866 678-6789

Calls will automatically be routed to the appropriate Regional or National AR Centre.

AR reports can also be mailed to the new centres at the following addresses:

Manitoba Regional Adverse Reaction Centre	Alberta Regional Adverse Reaction Centre
Rm. 114,	c/o Ste. 730,
510 Lagimodière Blvd.	9700 Jasper Ave.
Winnipeg MB	Edmonton AB
R2J 3Y1	T5J 4C3

Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Mefloquine: suspected association with QT prolongation

A 20-year-old man with no significant medical history and taking no other medications experienced prolongation of the QT interval after receiving Apo-Mefloquine, 250 mg once weekly for 4 weeks, for malaria prophylaxis. Two days after taking the fourth dose of mefloquine, he presented with dizziness, headache, nausea and tingling in the arms followed by a decreased level of consciousness. He became hypotensive and required hospital admission. An electrocardiogram (ECG) showed prolonged QT intervals (432 ms, 402 ms and 484 ms). The echocardiogram yielded normal findings. Information such as electrolyte levels and corrected QT intervals were not specified by the reporter. The mefloquine therapy was stopped, and the patient received an epinephrine infusion for a short period. An ECG repeated 8 days later showed a QT interval of 380 ms. Cases of QT prolongation during treatment with mefloquine have been described in the literature.[1,2]

References

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Summary of health professional and consumer advisories posted from Feb. 19 to May 16, 2005

Advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html

Date	Product	Subject and type
May 13	New Choice Pregnancy Test	Advisory not to use New Choice Pregnancy Test — consumer information
May 12	Diane-35	Diane-35: new warning — consumer information
May 12	Master's Miracle & Miracle II	Warning not to use Master's Miracle Fortified Mineral Neutralizer or Miracle II Miracle Neutralizer — consumer information
May 12, Apr 22, 15 & 14	Avandamet, Avandia, Coreg, Paxil, Paxil CR, Relafen and ratio-Paroxetine	Safety Information and update — consumer information update — consumer information — GlaxoSmithKline Inc. health professional communication — ratiopharm Inc. health professional communication
May 6	Xigris	Xigris: safety information — Eli Lilly Canada Inc. — health professional communication
Apr 29	Pms-Sodium Polysterene Sulfonate	Warning not to consume a certain lot of pms-Sodium Polysterene Sulfonate Powder for Suspension — consumer information
Apr 27	Elidel and Protopic	Elidel cream and Protopic ointment: safety information — consumer information
Apr 27	Trileptal	Trileptal: life-threatening dermatological reactions and multi-organ hypersensitivity — Novartis Pharmaceuticals Canada Inc. — health professional communication
Apr 26	Magnetic resonance imaging	Transdermal drug patches: thermal burns during magnetic resonance imaging (MRI) procedures — notice to hospitals
Apr 21	Bextra	Bextra: serious adverse drug reactions — Pfizer Canada Inc. — health professional communication
Apr 19	Blood glucose meters	LifeScan models of blood glucose monitoring systems: safety information — LifeScan — consumer information
Apr 18	Reminyl	Reminyl in mild cognitive impairment: investigational studies — Janssen-Ortho Inc. — health professional communication
Apr 7	Bextra and Celebrex	Sales suspension of Bextra and new restrictions on Celebrex — consumer information
Mar 31	Ergolift Patient Lifts	BHM Ergolifts: reliability of the actuator — notice to hospitals
Mar 24 & 23	Icodextrin	Icodextrin-containing peritoneal dialysis solutions: falsely elevated blood glucose monitor readings — consumer information and notice to hospitals
Mar 14	WT-5200 Warming Units	Electrically heated blankets: fire and burn risks — consumer information
Mar 12	Cough Syrup DM	Advisory not to use Cough Syrup DM DIN 02015781, lot numbers starting with 2J29 and 3J29 — consumer information
Mar 8 & 3	Crestor	Crestor: muscle-related adverse events — AstraZeneca Canada Inc. consumer information and health professional communication — consumer information
Mar 3	Ayurvedic products	Ayurvedic medicinal products: high levels of heavy metals — consumer information
Mar 3	Aristolochic acid	Reminder not to use products containing aristolochic acid — consumer information
Feb	Marquis ICD and CRT-D	Medtronic implantable cardiac defibrillators: safety information — Medtronic of Canada Ltd. — health professional communication

To receive the Newsletter and health product Advisories free by email, join Health Canada's ***Health_Prod_Info*** mailing list. ***Go to www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html***.

Newsletter and Advisories by email

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Marketed Health Products Directorate
AL 0701B
Ottawa ON K1A 0K9
Tel 613 954-6522
Fax 613 952-7738

Health professionals/consumers report toll free:

Tel 866 234-2345
Fax 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Editorial staff
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Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V)
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Expert Advisory Committee on Pharmacovigilance, Regional AR Centres and Health Canada staff

Suggestions?
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca

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(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

Date	Product	Subject and type
May 13	New Choice Pregnancy Test	Advisory not to use New Choice Pregnancy Test — consumer information
May 12	Diane-35	Diane-35: new warning — consumer information
May 12	Master's Miracle & Miracle II	Warning not to use Master's Miracle Fortified Mineral Neutralizer or Miracle II Miracle Neutralizer — consumer information
May 12, Apr 22, 15 & 14	Avandamet, Avandia, Coreg, Paxil, Paxil CR, Relafen and ratio-Paroxetine	Safety information and update — consumer information update — consumer information — GlaxoSmithKline Inc. health professional communication — ratiopharm Inc. health professional communication
May 6	Xigris	Xigris: safety information — Eli Lilly Canada Inc. — health professional communication
Apr 29	pms-Sodium Polysterene Sulfonate	Warning not to consume a certain lot of pms-Sodium Polysterene Sulfonate Powder for Suspension — consumer information
Apr 27	Elidel and Protopic	Elidel cream and Protopic ointment: safety information — consumer information
Apr 27	Trileptal	Trileptal: life-threatening dermatological reactions and multi-organ hypersensitivity — Novartis Pharmaceuticals Canada Inc. — health professional communication
Apr 26	Magnetic resonance imaging	Transdermal drug patches: thermal burns during magnetic resonance imaging (MRI) procedures — notice to hospitals
Apr 21	Bextra	Bextra: serious adverse drug reactions — Pfizer Canada Inc. — health professional communication
Apr 19	Blood glucose meters	LifeScan models of blood glucose monitoring systems: safety information — LifeScan — consumer information
Apr 18	Reminyl	Reminyl in mild cognitive impairment: investigational studies — Janssen-Ortho Inc. — health professional communication
Apr 7	Bextra and Celebrex	Sales suspension of Bextra and new restrictions on Celebrex — consumer information
Mar 31	Ergolift Patient Lifts	BHM Ergolifts: reliability of the actuator — notice to hospitals
Mar 24 & 23	Icodextrin	Icodextrin-containing peritoneal dialysis solutions: falsely elevated blood glucose monitor readings — consumer information and notice to hospitals
Mar 14	WT-5200 Warming Units	Electrically heated blankets: fire and burn risks — consumer information
Mar 12	Cough Syrup DM	Advisory not to use Cough Syrup DM DIN 02015781, lot numbers starting with 2J29 and 3J29 — consumer information
Mar 8 & 3	Crestor	Crestor: muscle-related adverse events — AstraZeneca Canada Inc. consumer information and health professional communication — consumer information
Mar 3	Ayurvedic products	Ayurvedic medicinal products: high levels of heavy metals — consumer information
Mar 3	Aristolochic acid	Reminder not to use products containing aristolochic acid — consumer information
Feb	Marquis ICD and CRT-D	Medtronic implantable cardiac defibrillators: safety information — Medtronic of Canada Ltd. — health professional communication

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Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
AL 0701B
Ottawa ON K1A 0K9
Tel 613 954-6522
Fax 613 952-7738

Health professionals/consumers report toll free:

Tel 866 234-2345
Fax 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Editorial staff
Ann Sztuke-Fournier, BPharm (Editor-in-Chief)
Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V)
Gilbert Roy, BPharm
Michel Gagné, BScPht
Sally Pepper, BScPhm

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Suggestions?
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.